TREAT TB | Technology, Research, Education and Technical Assistance for Tuberculosis

END OF PROJECT REPORT

Generating evidence to improve diagnosis and treatment of tuberculosis

USAID FROM THE AMERICAN PEOPLE

Vital Strategies

The Union

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ACKNOWLEDGEMENTS

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The STREAM clinical trial, a project under TREAT TB, was conceived of/designed by USAID and The International Union Against Tuberculosis and Lung Disease (The Union). Vital Strategies, an affiliate of The Union, is the Sponsor of the trial. STREAM Stage 1 was funded by USAID through the TREAT TB Cooperative Agreement, with additional support from the United Kingdom Medical Research Council (MRC) and the United Kingdom Department for International Development (DFID) under an MRC/DFID Concordat Agreement. STREAM Stage 2 is being funded by USAID and Janssen Pharmaceuticals, the maker of bedaquiline, with additional support from MRC and DFID.

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St. Peter's Tuberculosis Specialized Hospital

University of Stellenbosch

Warwick Medical School

Wits Health Consortium

Yale University School of Public Health

ACRONYMS

A-TRACTION	Asian Tuberculosis Research and Clinical Trials Integrated Organizational Network
CAB	Community Advisory Board
CE	Community Engagement
CLO	Community Liaison Officer
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DFID	Department for International Development
DOT	Directly Observed Therapy
DR-TB	Drug-Resistant Tuberculosis
ECG	Electrocardiogram
GF	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GPP	Good Participatory Practice
The Union	International Union Against Tuberculosis and Lung Disease
LSTM	Liverpool School of Tropical Medicine
LTBI	Latent TB Infection
MDR-TB	Multidrug-Resistant Tuberculosis
M&E	Monitoring and Evaluation
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London
NTP	National Tuberculosis Program
OR	Operational Research
PI	Principal Investigator
Pre-XDR-TB	Pre-Extensively Drug-Resistant TB
RESIST-TB	Research Excellence to Stop TB Resistance
SSTR	Standard Short Treatment Regimen for MDR-TB
STREAM	The clinical trial entitled “Evaluation of a Standardized Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis
SME	Supervision, Monitoring and Evaluation
TA	Technical Assistance
TREAT TB	Technology, Research, Education and Technical Assistance for TB
TB	Tuberculosis
TIME	Tuberculosis Impact Modelling & Estimates
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
WGS	Whole Genome Sequencing
WHO	World Health Organization

INTRODUCTION

Tuberculosis (TB) and drug-resistant TB (DR-TB) are major threats to global public health. For more than a decade, the Technology, Research, Education and Technical Assistance for TB (TREAT TB) project has sought to generate new knowledge to address these threats through clinical trials of priority research questions, targeted operational research, and field evaluations of diagnostic tools.

This final report documents TREAT TB activities, achievements, and lessons learned over the course of the 12-year project.

OVERVIEW OF TREAT TB

In 2008, USAID published a call for research proposals to respond to an urgent need to develop the evidence base to address gaps in TB research. The proposal selected was TREAT TB: Technology, Research, Education and Technical Assistance for Tuberculosis. TREAT TB was a multi-year project aimed at supporting research to optimize the effectiveness of existing technologies and approaches for TB diagnosis and treatment, while supporting late-stage clinical trials, field evaluations and operational research (OR) to bring new tools and approaches to the fore.

TREAT TB activities include the STREAM clinical trial, targeted OR, and technical assistance (TA) to national TB programs (NTPs). TREAT TB's approach was to build capacity where it worked to ensure sustainable impact, and to collaborate closely with affected communities to ensure they benefitted directly from TREAT TB. Since its launch, TREAT TB has informed global, regional, and country TB control efforts, generating important new knowledge and sharing its findings widely.

Key achievements of the project include contributing critical evidence for major global decisions about the treatment of multidrug-resistant TB (MDR-TB); dissemination of STREAM Stage 1 results in the *New England Journal of Medicine*[1] and the *Bulletin of the World Health Organization*;[2] supporting the Philippines' scale up of a shorter MDR-TB regimen; training more than 170 health professionals to conduct OR independently; development of a robust program of community engagement as part of the STREAM clinical trial; and making lessons learned from STREAM widely available to the global community to improve future research.

USAID's support of TREAT TB has been instrumental in catalyzing the introduction of better diagnostics and treatments for TB and MDR-TB.

Research Activities

STREAM CLINICAL TRIAL

OVERVIEW

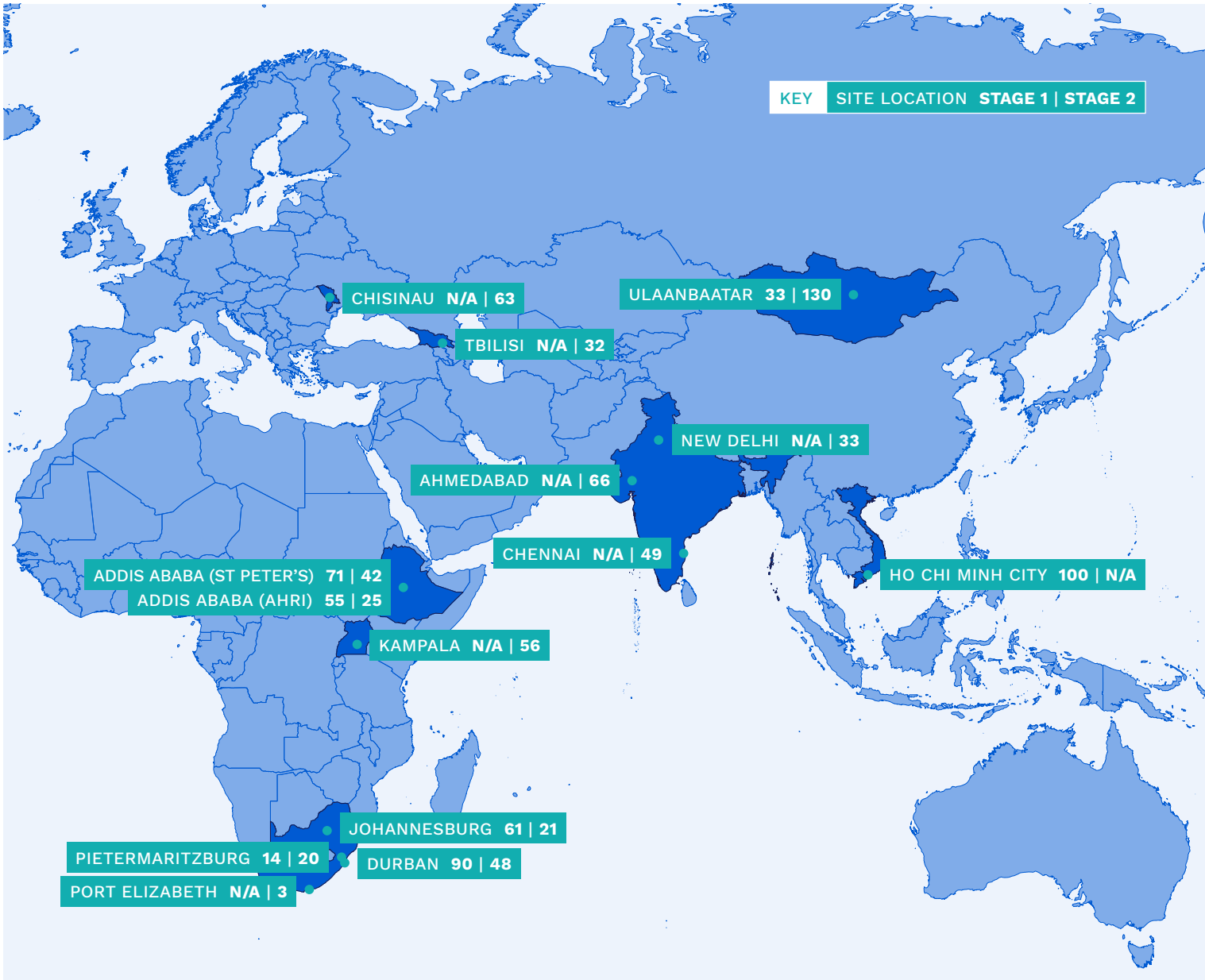
1,012

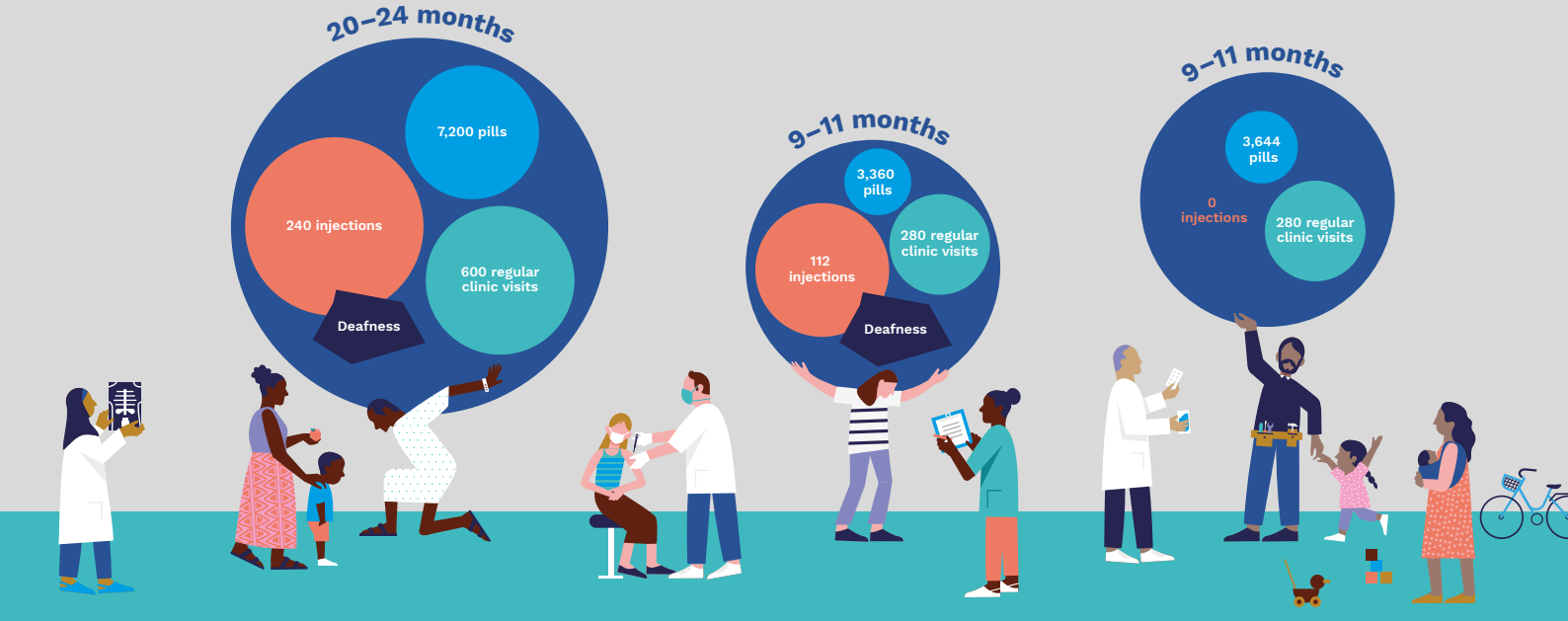
Number of participants recruited to STREAM

The STREAM *(Evaluation of a Standardized Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis)* clinical trial is the first large-scale, multi-country clinical trial to examine shortened regimens for MDR-TB. It is also the first phase III trial to test the efficacy and safety of bedaquiline in a shorter treatment regimen. In addition to evaluating the efficacy, safety and health economics of new MDR-TB regimens, STREAM has supported a robust program of community engagement, particularly at Stage 2 sites, and encouraged use of STREAM data for analyses of important secondary research questions.

The STREAM trial is comprised of two stages. Stage 1 began in 2012 as a pragmatic clinical trial. Stage 2, which added two bedaquiline-containing arms, resulted in STREAM becoming a United States Food and Drug Administration (US FDA)-regulated registration trial. The two stages of the trial recruited more than 1,000 participants at sites in Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, Uganda, and Vietnam, making STREAM the world's largest recruited clinical trial for MDR-TB.

BELOW
Number of STREAM trial participants recruited, by location





WHO 2011 20–24 month regimen
STAGE 1: CONTROL

Modified 'Bangladesh' regimen
STAGE 1: INTERVENTION
STAGE 2: CONTROL

All-oral, bedaquiline containing regimen
STAGE 2: INTERVENTION

ABOVE
The STREAM Trial: Regimens compared in STREAM Stage 1 and Stage 2

Stage 1

Aims of Stage 1

STREAM Stage 1 compared a 9–11-month MDR-TB regimen to the locally-used regimen in line with 2011 World Health Organization (WHO) guidance (approximately 20 months).[3] The aim of Stage 1 of the STREAM trial was to evaluate the efficacy, safety and cost of the two regimens.

The specific trial objectives were to:

- Assess whether the proportion of participants with a favorable efficacy outcome on the 9–11-month study regimen was not inferior to that on the 20-month regimen;
- Compare the proportion of participants who experience a grade 3 or greater adverse event during treatment or follow-up in the 9–11-month regimen to the control regimen; and
- Evaluate the cost of the two regimens, for both the participant and the health system (see the Health Economics section of this report for more details).

Results and findings

Efficacy and safety results from Stage 1 were published in the *New England Journal of Medicine*[1] in March 2019, and health economics results were published in February 2020 in the *Bulletin of the World Health Organization*.[2] The results demonstrated that:

- The STREAM 9–11-month regimen is non-inferior in terms of efficacy to the locally-used regimen in line with 2011 WHO guidance (approximately 20 months).[1]
- Overall, there were similar rates of severe adverse events between the 9–11-month regimen and the 20-month regimen, but there were differences in the types of adverse events caused by the two regimens.[1]
- Electrocardiogram (ECG) monitoring was very useful and was required throughout treatment. This was done during Stage 1 of STREAM but was expected to be more challenging in most routine program settings.
- The 9–11-month regimen provides cost savings to both patients and the health system, compared to the 20-month regimen (see more below under Health Economics).[2]
- The difference in treatment effect between the regimens did not differ based on HIV status.[1]

>90%

Participant retention rate for Stage 1

Until STREAM, there was a lack of strong supporting evidence to underpin MDR-TB treatment guidelines. The results from STREAM Stage 1 help to fill that gap.

I.D. Rusen
Project Director for TREAT TB

Stage 2

Aims of Stage 2

STREAM Stage 2 is ongoing. It is evaluating the efficacy, safety and cost of an all oral, bedaquiline-containing regimen that is potentially as effective as, and more tolerable than, injectable-containing regimens like the 9–11-month regimen evaluated in STREAM Stage 1. It is also evaluating a 6-month, injectable- and bedaquiline-containing regimen. The principal specific objectives of Stage 2 include:

- Assess whether the proportion of participants with a favorable efficacy outcome on a fully oral 9–11-month regimen (in which bedaquiline replaces kanamycin and is prescribed throughout the 9 months) is non-inferior to the 9–11-month regimen evaluated in Stage 1;
- Assess whether the proportion of participants with a favorable efficacy outcome on a 6-month, injectable- and bedaquiline-containing regimen is non-inferior to the 9–11-month regimen evaluated in Stage 1;
- Compare the proportion of participants who experience a grade 3 or greater adverse event during treatment or follow-up in the fully oral 9–11-month regimen to the control regimen;
- Compare the proportion of participants who experience a grade 3 or greater adverse event during treatment or follow-up in the 6-month regimen to the control regimen;
- Evaluate the pharmacokinetics of bedaquiline and M2 in participants randomized to the study regimens and assess pharmacokinetic/pharmacodynamics relationships of bedaquiline for safety and efficacy;
- Compare the economic costs incurred during treatment by participants and by the health system in the fully oral 9-11-month regimen compared to the control regimen; and
- Calculate the economic costs associated with the 6-month regimen and compare these with the control regimen.

Bedaquiline-containing, all-oral MDR-TB regimens like the one being evaluated in Stage 2 are already being introduced based on the experience of NTPs, but there is currently no published clinical trial evidence regarding their efficacy, safety, or cost-effectiveness. Stage 2 of STREAM will help address this gap by generating high-quality evidence that could influence future guidelines and decision-making about MDR-TB treatments.

588

Number of participants recruited to STREAM Stage 2

SIGNIFICANT STAGE 2 MILESTONES

April 2016
STREAM Stage 2 enrolled its first participant at the National Centre for Communicable Diseases in Ulaanbaatar, Mongolia

June 2017
100th participant was enrolled at King DinuZulu Hospital in Durban, South Africa

February 2019
400th participant was enrolled at BJ Medical College and Civil Hospital in Ahmedabad, India

January 2020
Enrollment completed, with a total of 588 participants randomized to all arms of the trial

January 2021
Last-recruited participant completed their allocated trial treatment regimen

2022
Primary results from Stage 2 of the trial expected

RIGHT
From Left to Right: Sarah Meredith, Francesca Conradie, Bazra Tsogt, Andrew Nunn, Bertie Squire, I.D. Rusen and YaDiul Mukadi presenting final STREAM Stage 1 results at the 49th Union World Conference on Lung Health in The Hague, Netherlands

ACHIEVEMENTS

The STREAM clinical trial has influenced policy and program decisions about the use of shorter treatment regimens for MDR-TB at both the global and national level. In addition, the trial, which has been ongoing for more than 10 years in eight countries, offered an exceptional opportunity to evaluate key operational successes related to trial design and implementation.

78.8%

Percentage of Stage 1 participants in the study arm with a favorable outcome

Impact on Policy and Programs

In early 2012, when the trial began, the standard of care for MDR-TB lasted up to 24 months, included an injectable agent, and had an average success rate of just over 50%.[4] Although the WHO began recommending shorter treatment regimens in 2016, the Guidelines Development Group acknowledged the very low certainty in the evidence underpinning their recommendations due to a lack of randomized clinical trial data.[5] Results from Stage 1 of STREAM filled that gap, providing high-quality evidence that contributed to the WHO's strengthened recommendations regarding the use of shorter regimens.

In 2017, following release of STREAM Stage 1 preliminary results, the WHO stated:

"The World Health Organization welcomes the release of the interim results from the STREAM Stage 1 MDR-TB randomised clinical trial and looks forward to the release of the final data and analysis... The STREAM trial – the first randomised controlled trial to test the efficacy, safety and economic impact of a standardised shorter MDR-TB regimen – demonstrates the value and importance of assessing treatment regimens in Phase III clinical trials to fully understand their potential and limitations."[6]

When the WHO confirmed its recommendation for use of a standardized shorter treatment regimen in a December 2018 update to the MDR-TB treatment guidelines,[7] it again cited STREAM results as an important source underlying its recommendation.

When recommending guidelines for the shorter regimen, the WHO clearly mentioned evidence from STREAM Stage 1. The Ethiopian National Tuberculosis Program also asked about our experience with the shorter regimen evaluated in STREAM. We shared our experiences and were actively involved in the design and revision of the national guidelines when Ethiopia adopted the shorter regimen in April 2018.

Dr. Daniel Meressa
Principal Investigator, St. Peter's Tuberculosis Specialized Hospital, Addis Ababa, Ethiopia

1.1m

Number of pills supplied without interruption during Stage 2

Operational Highlights

- STREAM successfully implemented a public/private partnership in the context of a complex licensing trial, navigating the stringent regulatory requirements of the US FDA and the European Medicines Agency.
- With more than 1,000 participants recruited to both Stages of the trial, STREAM is the largest recruited MDR-TB trial to date. The trial's commitment to local buy-in for the trial and careful consideration of NTP referral patterns were pivotal for ensuring the trial was able to recruit enough participants.
- Even during the COVID-19 pandemic, Stage 2 trials sites were able to dispense all doses of study treatment to trial participants without interruption. This was due, in part, to a COVID-19-mitigation strategy that continually assessed local situations and adapted accordingly – for example, where participants were unable to travel to the trial site due to restrictions, study teams delivered participants' medications.
- Clinical trial institutions are stronger after STREAM and will make future TB trials easier to conduct at STREAM sites. We attribute this in part to USAID's unwavering support for TREAT TB's capacity building and sustainability-focused efforts.
- The trial supplied all 13 medications (in total, more than 1.1 million pills) required for the trial without a single stockout. Quality-assured suppliers were pre-qualified, and Sponsor pharmacists pre-positioned sufficient quantities of trial medicines in regional depots to help address uncertainties in recruitment, manufacturer lead-times and regulatory approval timelines.
- Final participant retention rates in Stage 1 of the trial exceeded 90%, which is a tribute to the excellent care and follow up provided by the STREAM trial sites.

BELOW
STREAM trial participant completing a hearing test at the National Centre for Communicable Diseases in Ulaanbaatar, Mongolia

LESSONS LEARNED

The STREAM clinical trial offered an exceptional opportunity to evaluate key issues related to trial design and implementation and make practical recommendations to improve future trials.

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Deep local knowledge and stakeholder relationships are essential for successful implementation. There were 15 STREAM trial sites from eight countries in Africa, Asia, and Europe – all with very different local contexts. It has been essential to the success of the trial to understand local variations and effectively adapt implementation in response.

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Sponsors should systematically assess potential sites and develop a targeted response to identified weaknesses. A robust site selection process is required to ensure appropriate sites are selected and equipped to manage a clinical trial. The process should consider patient population (recruitment potential), clinical expertise (ability to manage participant care), microbiology expertise, non-clinical expertise (e.g., project management and regulatory knowledge and experience), and physical infrastructure (such as that of lab, pharmacy, and information technology). When weaknesses are identified, mitigation plans should be developed and implemented.

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Site staff must have a broad range of skills and experience to effectively implement a phase III clinical trial. Good clinicians are essential for successful trial implementation, but a wide range of other skills are needed, including project management skills, ethics and regulatory expertise, and data management experience. Sponsors should ensure principal investigators (PIs) fully understand the breadth of trial requirements so that appropriately trained staff are identified and retained.

—

Implement a well-designed, risk-based monitoring strategy. Oversight of a clinical trial requires a well-designed, risk-based monitoring strategy that is flexible enough to account for the different experience/expertise levels of trial sites. While much of the oversight can be conducted remotely, onsite visits are required to build personal relationships, effectively build capacity, review sensitive participant records and observe site facilities and activities.

—

Sites should develop and document standard processes in line with the trial protocol for key aspects of trial implementation. Regulated clinical trials must meet the highest standards related to participant safety and data integrity. To do so, trial sites must develop and implement locally appropriate standard processes to ensure proper adherence to trial requirements.

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Sponsors should seek and consider local input on trial design before finalization with central regulators. Sponsors should aim to maximize site-level consultation on major trial decisions, especially around trial regimens, safety assessments and central laboratory requirements. Although this could delay central approvals, it might also significantly improve implementation by avoiding decisions that may be non-negotiable in some countries or sites.

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Roles and responsibilities must be clearly delineated and communicated to avoid inefficiency and gaps in implementation or oversight. Implementation of phase III registration trials typically involves multiple partners, creating the risks that key activities are not completed or that partners duplicate efforts. It is therefore essential to clearly delineate roles and responsibilities at the start of the trial, and systematically oversee partner activities.

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Document and implement well-designed data flows. The collection of trial data requires integration of data from multiple sources. These data may be generated at different times and in different formats and may change over time as protocol versions and trial design evolve. This makes it important to implement robust, flexible and locally appropriate data management systems, and to have well-qualified data management staff in place.

—

Robust forecasting is needed to ensure continuous availability of clinical supplies. MDR-TB clinical trial supply chain management must consider complicated study regimens, in addition to complex, varied and evolving importation requirements. To avoid treatment interruptions, sufficient stocks must be continuously available, while minimizing costs, storage, and waste due to expiry. This requires the development of a robust forecasting system and continuous monitoring of supply chains.

—

Ensure the supply chain management system has adequate procedures and resources in place. Local pharmacy processes need to be developed to implement protocol/central trial requirements in a manner appropriate for the trial site context. In STREAM, both central and site level standard procedures were developed, and local resources were provided to ensure compliance.

STREAM HEALTH ECONOMICS

OVERVIEW

Health systems in many high MDR-TB burden countries face resource constraints, making economic evaluations of treatment options essential to efficiently allocate resources. Moreover, global health policy goals, including the End TB targets, emphasize financial protection for patients and the elimination of catastrophic healthcare costs. The STREAM economic evaluations aim to provide evidence to help guide policies that address these priorities.

$238

Stage 1 participant cost savings from study regimen

Stage 1

Aims of Stage 1

The principal objective of the economic evaluation in Stage 1 was to document how a shortened MDR-TB treatment regimen (as compared to the longer control regimen) affected the amount, nature and timing of costs incurred by trial participants and by the health system.

Results and findings

Stage 1 health economics data were collected in Ethiopia and South Africa. The Stage 1 health economics results, published in February 2020 in the *Bulletin of the World Health Organization*, demonstrated that the shorter 9–11-month regimen significantly reduced the cost of treating MDR-TB for both participants and health systems compared to the 20-month regimen.[2]

The health system cost reduction per participant was around US $1,545 (25%) in Ethiopia and around US $1,722 (21%) in South Africa. Clinical and health system factors, such as wages, prices and models of care influenced savings. Although participants on the shorter regimen needed cardiac monitoring due to the increased risk of QTc prolongation, the cost of US $150 per participant monitored was greatly outweighed by other savings.[2]

The shorter regimen also led to reduced participant expenditure (US $574 long vs. US $238 short regimen) and increased earning capacity. In Ethiopia, participants on the shorter regimen reported reductions in dietary supplementation expenditure, and greater productivity over the 132 weeks of treatment and follow-up with an additional time worked of 667 hours. Participant cost savings also arose from reduced visits to health facilities over the treatment course.

Using published estimates of mean income for a typical person in Ethiopia, the trial estimated the mean cost of treatment to trial participants in Ethiopia was between 30% and 50% of their income. When compared to the WHO recommended threshold of 20%, this indicates that a substantial number of participants experienced catastrophic costs. However, lower expenditure (US $238 lower) and increased productivity for participants on the shorter regimen indicate the shorter regimen may help reduce catastrophic costs significantly. This is a key objective of the Sustainable Development Goal 3.3 to end the TB epidemic by 2030 and the End TB target to ensure that no family is burdened with catastrophic expenses due to TB.

Stage 2

In 2020, the WHO recommended the use of shorter, all-oral, bedaquiline-containing regimens for patients with MDR-TB.[8] In addition to its clinical benefits, it was thought the all-oral treatment would reduce costs of MDR-TB treatment from both a health system and patient perspective. However, there was no high-quality evidence to support this hypothesis. Stage 2 of STREAM will provide within-trial evidence relating to the health system and patient costs of a 9-month all-oral, bedaquiline-containing regimen (vs. a 9-month injectable containing regimen) to address this gap.

There is also no high-quality evidence to show the economic implications of shorter regimens at the country level – which will vary considerably between countries due to the local context. Because Stage 2 of STREAM is collecting health economics data at seven sites in a diverse range of countries (Ethiopia, India, Moldova and Uganda), the results will be important for showing variations across countries in terms of costs and savings both to participants and health systems. This will provide useful additional information to NTPs when considering how to implement a shorter, all-oral regimen.

RIGHT
Professor Bertie Squire, Liverpool School of Tropical Medicine, presenting at the 49th Union World Conference on Lung Health in The Hague, Netherlands

ACHIEVEMENTS

Impact on Policy and Programs

The STREAM health economics results were considered and cited in connection with two updates to the WHO guidance on management of MDR-TB[9] and the WHO 2019 consolidated guidance,[10] which endorsed shortened regimens in part due to the economic benefits for both patients and health systems.

$1,500

Per participant health system savings from STREAM Stage 1 study regimen

Operational Highlights

- The STREAM health economics study was the first to estimate the costs incurred by both participants and the health system within a phase III MDR-TB randomized clinical trial.
- The inclusion of a health economics evaluation as part of STREAM demonstrates it is possible to incorporate health economics into a phase III MDR-TB trial and has numerous benefits. For example, use of an integrated STREAM informed consent document meant that participants only had to consent once to take part in both the clinical and health economics components of the trial. This reduced health workers' workload and underscored for participants that health economics is an integral part of the overall trial.
- STREAM is the first health economic study conducted at some STREAM sites – helping to build much needed capacity for future health economic studies at these locations.
- The trial's focus on capacity building as part of the health economics study will have longer-term benefits to trial sites. At each site, a health economics focal person(s) was recruited and received continuous support and training from the study team covering topics including best practices in defining, collecting, and categorizing different types of costs; query management; assessing data quality; and conduct of participant interviews (particularly around sensitive topics). This investment in human resources positions STREAM sites to participate in future health economics studies.
- The trial's commitment to collaboration helped ensure the COVID-19 pandemic had no significant impact on implementation of the health economics study. During the pandemic, data collection has been carried out by phone, rather than in person, and only one participant could not be contacted to provide data. A "COVID-19 diary" is being kept at each site in order to track the principal COVID-19-related events. This information will be used to assess whether the pandemic has affected participant spending patterns and to aid interpretation of the pandemic's impact on participant costs.

LESSONS LEARNED

STREAM offered a unique learning opportunity, leading to important lessons learned and practical recommendations, including:

329

Number of Stage 2 participants in the Health Economics study

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Develop a publication strategy that improves placement of health economics results. Given the importance of health economics to policy making, ideally health economics results would be published alongside clinical trial results. However, this is not possible in all scientific journals and can require trial investigators to take a number of preparatory steps. Based on the STREAM experience, we recommend investigators identify journals that have published both clinical and health economics results, and prioritize those journals for consideration. We also recommend that health economics study protocols are published separately from related clinical protocols.

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Data collection must be adapted to the local setting. Given the volume and sensitive nature of information collected, it is important to consider when, where and how health economics data are collected and to allot adequate time for collection. For example, in South Africa, some Stage 1 questionnaires were only partially completed because participants rushed to use free transport back to their homes. Based on the Stage 1 experience, Stage 2 data collection processes were adjusted, enabling the trial to successfully collect health economics data from all participants who attended in-person assessments, as well as over the phone during the COVID-19 pandemic.

—

Continuous support for site health economists and robust oversight of data collection are essential for ensuring data quality. Although most health economics interviews were conducted during clinical assessment visits, there were initially delays in integrating health economics data into the trial database. This made timely monitoring of data queries difficult. To address this, a robust monitoring process was implemented with daily checks. Continuous focus on data quality via onsite visits, ad hoc and spot checks was also important. This process significantly reduced the number of open queries and the time taken to resolve these. By understanding and following the above processes, the capacity of individuals and sites to participate in trials was also improved.

—

Regular in-person monitoring visits are important. While remote monitoring can supplement in-person site visits, in-person monitoring by study coordinators is key to understanding local processes and identifying gaps and weaknesses. For example, one site initially experienced delays in addressing database queries from the study coordinator. During an in-person visit, the study coordinator discovered the site lacked a structured storage system for trial case report forms (CRFs), which made responding to queries inefficient. During the visit, the study coordinator worked with the site to develop an appropriate storage system for CRFs and data query resolution improved thereafter.

COMMUNITY ENGAGEMENT

OVERVIEW

Community engagement (CE) is an ethical obligation and an integral part of TB research. It can improve trial implementation and participant outcomes by building trust between affected communities and trial implementers. It also allows affected communities to participate in all stages of the research cycle – from setting the research agenda through to evidence-based policy change based on research results.

12

Number of CABs formed with STREAM support

A comprehensive program of CE was supported by the STREAM clinical trial at all 13 Stage 2 sites with the objective of:

- Raising awareness of TB and the trial and making complex information accessible to affected communities;
- Providing psychosocial support to trial participants and family members, which can help improve retention and adherence rates; and
- Creating a critical feedback link between affected communities and trial staff to ensure community views on key implementation issues were communicated and considered.

As part of STREAM's support for CE:

- CABs, comprised of representatives from non-governmental and community-based organizations, TB survivors and other community representatives, were established and supported as coordinating mechanisms for CE at all trial sites;
- Local CAB coordinators were chosen from CAB members, with the support of the trial team;
- A community liaison officer (CLO) was appointed at each site to act as a bridge between CAB members and the study team;
- Funding was provided for CE activities developed by the CABs, including feedback to and from the study team regarding STREAM, stakeholder meetings, CAB member training and capacity building, attendance at health policy meetings, community outreach, psychosocial support for STREAM participants, and cross-site experience sharing; and
- Technical assistance and CE coordination were provided to CABs by Vital Strategies and partners, including REDE-TB and Wits Health Consortium.

ACHIEVEMENTS

The commitment to CE throughout Stage 2 of the STREAM trial yielded significant achievements including development of program design tools, contributions to the creation of sustainable CE institutions, and improvements in STREAM trial implementation.

Impact on Policy and Programs

Although there are accepted principles confirming the need for CE in TB trials (for example, the *Good Participatory Practice (GPP) Guidelines for TB Drug Trials 2012*),[11] there are limited practical resources available to trial stakeholders to guide development and implementation of CE activities. The STREAM trial's focus on developing and documenting its experience means that new tools will be available for future TB trials seeking to implement impactful CE programs. In addition, the trial's focus on sustainability of CE institutions should contribute to better and more durable CE programs at STREAM sites and globally.

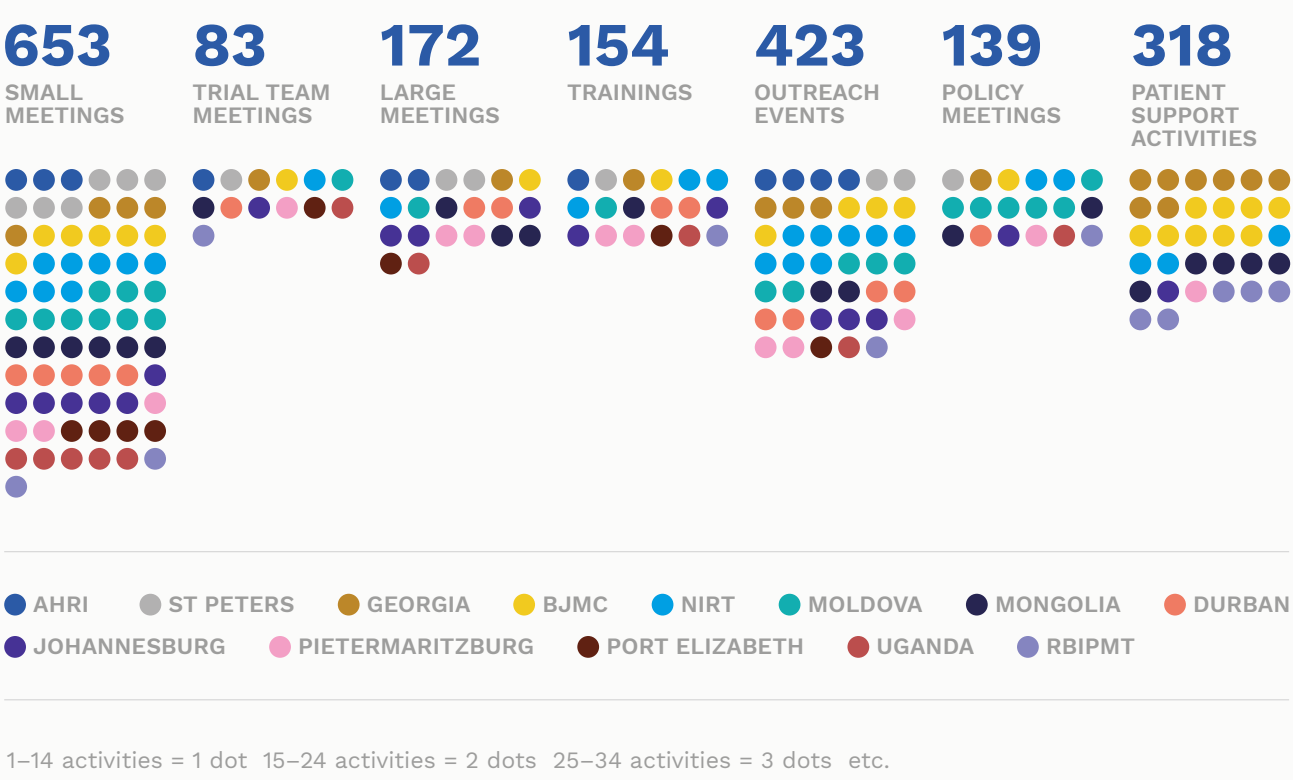
Key STREAM contributions include:

- **Documentation of recommendations and lessons learned.** STREAM was a comparatively large CE program, and therefore provided a unique opportunity to assess successes and challenges, as well as to make recommendations for future trials. STREAM's practical recommendations are summarized below and can be accessed in full here. The STREAM CABs' recommendations for effective CE can be found here.
- **Development of a logic model.** Logic models are important when designing a program or intervention to ensure the objectives of the program are clear and to develop a "theory of change" connecting activities with desired outcomes. During a participatory process, STREAM CABs developed a logic model for CE in a TB trial, which is available here.

Since the outset of the trial, USAID has been extremely supportive of efforts to build a comprehensive CE program, enabling the trial to generate and disseminate important information for donors and clinical trialists about the importance of CE in a clinical trial.

I.D. Rusen
TREAT TB Project Director

RIGHT
CE members working together to identify the main challenges addressed by STREAM CE in Hyderabad, India, 2019



ABOVE
Summary of community engagement activities from STREAM Stage 2

154

Number of CAB trainings completed

Operational Highlights

- Vital Strategies and its partners worked systematically with CABs to ensure members continue to participate in CE after STREAM funding ends. Of the 13 STREAM Stage 2 CABs, more than half have achieved at least one indicium of "sustainability" (defined as CAB membership on research and advocacy institutions, establishing structures necessary for ongoing CAB operation after funding from STREAM ends, and/or obtaining funding for non-STREAM activities). This should help ensure CABs are equipped to advocate for program and policy change based on Stage 2 results, and that capable CE partners exist at STREAM sites to serve as key partners in future TB trials.

- Community members are better able to participate as equal partners in clinical research due to STREAM CE. Since 2017, CAB members have completed more than 150 trainings about TB, TB research and CE, improving their capacity to participate at all stages of the research cycle.

- STREAM CABs have raised community awareness of TB and research, helping to ensure those most affected by TB research understand its implications and help ensure it is relevant and acceptable. Since 2017, STREAM CABs and trial sites have held more than 420 community outreach events often combined with TB or HIV screening.

- A global network of CE advocates has been created. The trial implemented a number of events and strategies designed to create a global network of advocates that will survive beyond STREAM.

  - The trial invited CAB members to international conferences to build capacity around TB and research, held in-person workshops for CAB members from STREAM sites to develop tools and share experiences, and sponsored experience sharing between CAB members at different trial sites.

  - The trial also designed a two-year cross-site webinar series covering nine sessions on topics ranging from the WHO guideline development process to the role of community members in ethics committees. In addition to building capacity, these sessions helped to create durable connections between CAB members that should encourage consultation and experience sharing after STREAM ends.

LESSONS LEARNED

423

Number of community outreach activities completed

>50%

Percentage of CABs achieving indicia of sustainability

—

Key stakeholders must understand and commit to the principles underlying community engagement to achieve its benefits. To achieve the benefits of CE, key stakeholders must commit to the principles set out in the *GPP Guidelines for TB Drug Trials 2012*.[11] STREAM's commitment to those principles – respect, fairness, integrity, transparency, accountability and autonomy – yielded important and long-term successes, including the development of highly productive working relationships between STREAM CABs and study teams, as well as creative stakeholder collaborations on complementary activities.

—

Roles and responsibilities of all stakeholders must be agreed by all key stakeholders. CE was a new practice for most STREAM sites, requiring the STREAM CABs and study teams to define and agree their roles and responsibilities. Through a structured program of CE, stakeholders successfully built an understanding of how their respective knowledge and skills were complementary and could be employed to improve trial implementation. In most cases, this meant involving CAB members as trusted partners for community outreach and (at some sites) participant support (financial and/or psychosocial). Study teams invested in training CAB members to maximize their ability to participate as full partners throughout the clinical research cycle.

—

Meaningful community engagement requires regular, open and honest communication between CABs and PIs/Sponsor. In any clinical trial, researchers have important knowledge and information that the community stakeholders do not, and the same is equally true for community stakeholders. Therefore, to optimize trial implementation and impact, there must be regular and open two-way communication between the study team and the community. This will also build trust between researchers and community members, which will have important long-term benefits for future research.

—

Research will be more relevant and acceptable if CABs/community members are involved throughout the research cycle. Ethical research must be both relevant and acceptable to the community where it is conducted. Therefore, it is important for sponsors to consult CABs (as community representatives) before, during and after a trial to ensure the trial addresses the health priorities of the community, trial documentation and procedures are culturally appropriate, and community members are equipped to advocate for better programs and policies.

—

Research will be more responsive to community needs if CAB membership is representative. CE mechanisms – like CABs – are an effective way to ensure researchers understand the views of the local community and those affected by the research being conducted. However, this will only be true when CAB membership is representative of the community where a study takes place. CAB members should therefore be drawn from and chosen by the community they represent.

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It is essential to increase CAB knowledge about research, TB, and community engagement. CAB members are not typically TB researchers, and therefore may have limited knowledge about research or clinical management of TB, which is needed in order to make meaningful contributions to trial design and implementation. It is therefore incumbent on sponsors and researchers to capacitate CAB members. The STREAM trial supported a multi-faceted program of capacity building for CAB members that included both locally-organized trainings and centrally-led experience sharing and capacity building events.

—

Community engagement processes must empower CABs to act autonomously and share community views. The ultimate objective of CE is to foster independent input into the research process by the community where it is conducted. However, CAB autonomy can be hard to achieve because reliance on the sponsor for funding and on researchers for information and training can contribute to a significant imbalance of power that is difficult for CABs to overcome. To mitigate the impact of significant Sponsor involvement, STREAM implemented an intensive CAB capacity building program, and STREAM CABs had significant freedom to choose and implement CE activities that responded to their local priorities and conditions.

—

Community engagement needs to be monitored and evaluated. There is limited evidence regarding the impact of CE, as it is a relatively recent part of TB clinical research. Evaluations of the impact of CE are therefore essential to convince donors and other stakeholders that meaningful CE is worth the required time and investment.

DISSEMINATION OF TRIAL RESULTS

OVERVIEW

The dissemination of research results is an important first step to achieving knowledge translation, building trust, and influencing policy. Stage 1 results were pre-released to the WHO for consideration in the context of their guideline development process. In addition, Stage 1 results were announced to global stakeholders at the 48th Union World Conference on Lung Health in 2017[12] and later published in the *New England Journal of Medicine*[1] and the *Bulletin of the World Health Organization*,[2] accompanied by media outreach, policy briefings, newsletters, and digital distribution.

At trial site locations, Vital Strategies developed and implemented a multi-pronged strategy to disseminate Stage 1 results to all key stakeholders, including trial teams, ministries of health, CABs/CLOs, trial participants, family members and other community stakeholders. Results were disseminated to PIs through webinars led by Vital Strategies and MRC CTU at UCL. Trial teams then disseminated results to CE stakeholders, including CABs/CLOs – typically at in-person meetings. Study teams and CABs communicated results to participants either at large dissemination events designed as celebrations, or in one-on-one meetings between study teams and participants.

ACHIEVEMENTS

Effective dissemination plans require consideration of messages, audiences, materials, and channels – in order to reach the diverse audiences interested in the results. In particular, dissemination of results to research participants is complex and sometimes overlooked. The STREAM dissemination plan was effective at reaching all key stakeholders – ranging from policy makers, such as the WHO, to trial participants and community members.

Impact on Policy and Programs

The objectives of dissemination to policy makers are knowledge translation and policy change. The objectives of dissemination to research participants and community members are to build trust and equip them to participate in decision-making processes and influence change. These objectives were achieved in the following ways:

- As discussed above, dissemination of the STREAM Stage 1 results to the WHO had an important impact on new MDR-TB treatment guidelines. Publication of the results in the *New England Journal of Medicine*[1] and the *Bulletin of the World Health Organization*[2] also made them widely accessible to the scientific community.
- At the community and participant level, the most important indicators of the impact of the trial's dissemination strategy were demonstrated in the feedback received from trial participants and community members, both of whom indicated they valued the inclusive nature of the STREAM dissemination events and access to study teams to discuss the results.

Operational Highlights

- The audience for STREAM dissemination activities was broad and inclusive. It included study teams at all Stage 1 and 2 sites, and participants/ community members at 14 of 15 trial sites.
- The community-targeted dissemination materials were made available in the primary local language of most STREAM sites, helping to improve accessibility of the dissemination materials and the results.
- Dissemination of the results to community members was evaluated in order to improve dissemination of Stage 2 results.

BELOW
Samantha Kozikott, Technical Officer from Vital Strategies' Research Division, presents on the evaluation of dissemination of preliminary results from STREAM stage 1, Hyderabad, India

LESSONS LEARNED

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Tailor strategies for different audiences. Stakeholders vary in terms of technical and scientific knowledge, cultural norms, and preferences. Therefore, dissemination strategies, materials and channels should be tailored to each target audience.

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For trial participants, ensure results are relevant. Statistical concepts may not be relevant to participants, who can be more interested in how trials affect them personally – for example, whether the study regimen "worked" and what side effects people experienced on the trial regimen.

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Use clear and simple materials that are tailored in terms of level of information and language to the target audience.

—

CABs and/or community members should help develop and pre-test participant/community member materials to ensure they are relevant and understandable. They are uniquely placed to know how participants and the community members will perceive and understand complex results.

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Results should be presented in the local language.

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It is useful to have physicians involved in the results dissemination due to their familiarity with the subject and their position of trust.

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Involve creative professionals and colleagues from communication, art, or journalism disciplines to help design appropriate dissemination materials. For trial participants and community members, consider emphasizing visual materials, such as videos and posters, rather than dense written materials and PowerPoint presentations.

—

Deliver results to participants and community members in safe, non-stigmatizing spaces. This can encourage questions/answers to improve understanding of the results, as well as build trust between researchers and communities.

RIGHT
YaDiul Mukadi of USAID (center) speaking at the panel discussion, "Improving dissemination of clinical trial results – experiences in TB and HIV clinical trials" at the 49th Union World Conference on Lung Health, The Hague, Netherlands

SECONDARY ANALYSES WITH STREAM DATA

OVERVIEW

10

Number of STREAM investigators who identified secondary research questions for analysis

Since publication of the Stage 1 results in the *New England Journal of Medicine*[1] and the *Bulletin of the World Health Organization*,[2] additional research questions have been identified for analysis using STREAM Stage 1 data. Results of those secondary analyses have been reported as abstracts or poster presentations at international conferences and in scientific journals. In 2020, *BMC Medicine*[13] published the results of an analysis of the efficacy of the Stage 1 long and short regimens using alternative outcome definitions. The results of that analysis indicate that the two regimens had similar outcomes. However, the risk of failure or relapse was slightly higher in the shorter regimen, which highlights the need to appropriately account for loss to follow-up and censoring in analyses.

RIGHT
STREAM Investigators Drs. Joanitah Nalunjogi, Daniel Meressa Kokebu, Dat Phan Dong, and Mekonnen Teferi (left to right) mark selection of their research questions

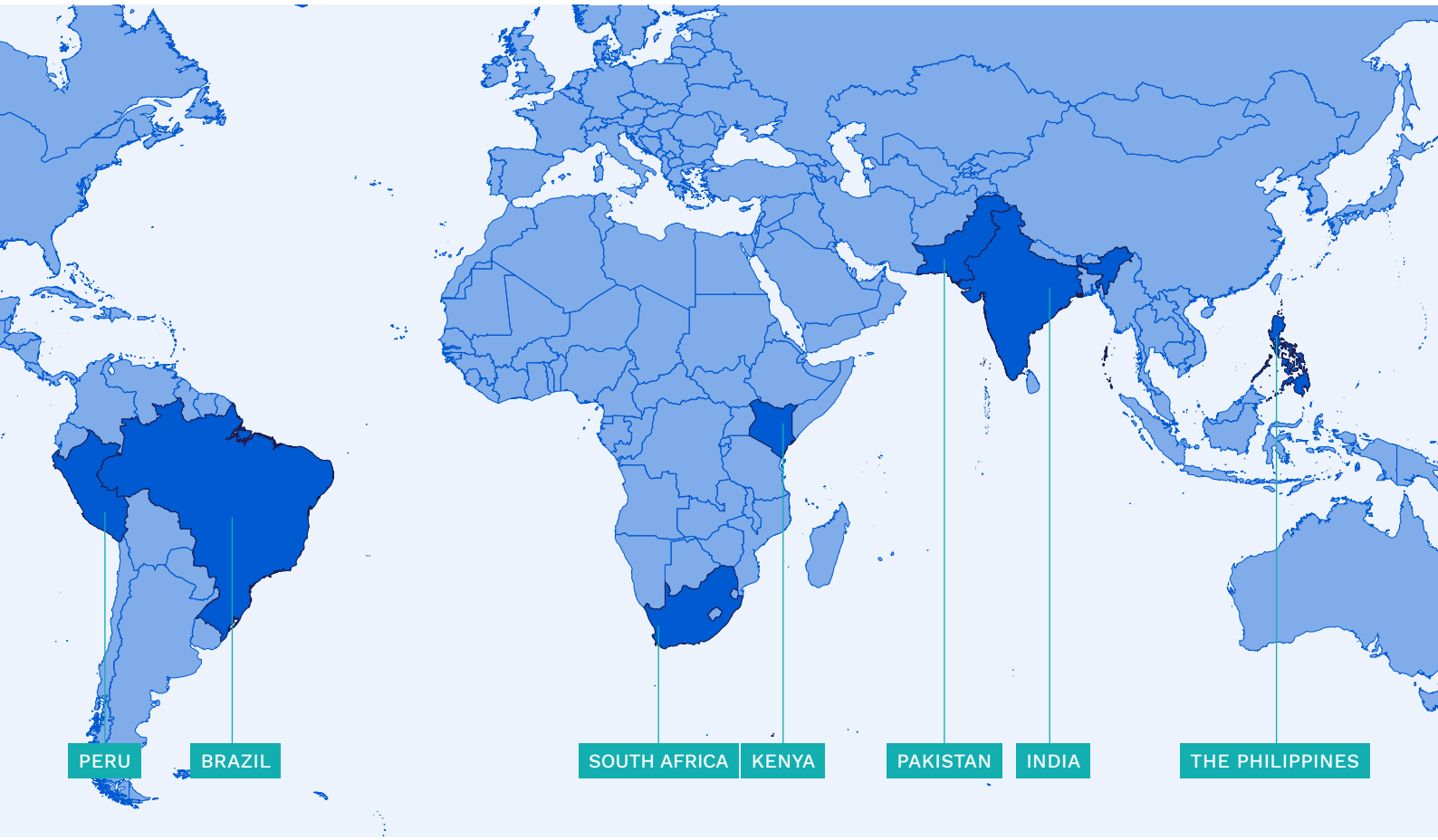
Several other secondary analyses are currently in progress. For example, diabetes mellitus is associated with adverse treatment outcomes in patients with drug-susceptible TB, but there is limited evidence on the effect of diabetes mellitus on patients with MDR-TB. Stage 1 data are now being analyzed to describe the outcomes of participants with self-reported diabetes compared to those without. In addition, gender-based differences in Stage 1 outcomes are being explored. An analysis of the predictors of QTc prolongation among participants on the short regimen, and predictors of outcomes are also underway, and analyses of microbiological data are also in progress. Results from these studies may provide important information for NTPs and policy makers on the use of the shorter regimen.

The anonymized STREAM Stage 1 dataset will be available to access through the Critical Path Institute (C-PATH) for non-commercial TB research by qualified researchers. This will facilitate the use of the STREAM Stage 1 data to answer important research questions and ensure TREAT TB's ongoing impact and contribution to the global TB community.

OPERATIONAL RESEARCH

OVERVIEW

Operational research (OR) is research applied to better understand complex systems and to support decision making. OR differs from clinical research by focusing on improving the health system or program in which the research is conducted. In the case of TB, there is a particular need to understand health systems in settings with a high burden of TB. Locally relevant OR is essential for influencing national policy and TB programs, and it is vital to improve research capacity in these settings.



ABOVE
Countries where health professionals participated in TREAT TB OR courses

TREAT TB delivered a number of OR training programs to ultimately improve local health systems by ensuring that health professionals have strengthened capacity in this important field of research.

TREAT TB utilized a combination of synchronous and asynchronous approaches to increase access to OR training while allowing participants to remain in their communities and workplaces. Since its launch in 2008, TREAT TB has provided health professionals in Brazil, India, Kenya, Pakistan, Peru, the Philippines and South Africa with the training needed to conduct high-quality operational research independently. In addition, our interactive e-tool and guidebooks on OR are freely accessible to researchers globally. Most recently, our work has focused on Peru and the Philippines.

TB is a major public health challenge in Peru. The 2014 notified case rate for TB was 97 per 100,000, with over 1,000 cases of MDR-TB.[14] To address the high burden of TB, in partnership with The Union and the NTP of the Peruvian Ministry of Health, TREAT TB launched an OR training course in September 2015. The course aimed to develop skills among health professionals to conduct OR studies independently and generate evidence to improve TB control.

In the Philippines, MDR-TB is a particular challenge, with an estimated 17,000 cases in 2015.[15] In collaboration with The Union, in 2016, TREAT TB launched a comprehensive package of technical assistance (TA) to the Philippines NTP to support national scale-up of the standard short treatment regimen (SSTR) for MDR-TB. OR training was a key focus of the TA package.

>45

Number of manuscripts published

RIGHT
Operational Research course, The Philippines

ACHIEVEMENTS

Our OR training has led to a larger pool of health professionals able to independently undertake locally relevant OR leading to improved health services. This has resulted in the publication of a significant amount of important research (See Appendix). Highlights of the impact of our OR training both in terms of policy and operational impact are outlined below.

>170

Number of health professionals trained

Impact on Policy and Programs

In October 2017, course participants from Peru presented their findings at the 48th Union World Conference on Lung Health in Guadalajara, Mexico. Four manuscripts were published in 2018; three in the *International Journal of Tuberculosis and Lung Disease*[16, 17, 18] and one in *PloS One*.[19]

Importantly, results from the studies informed policy decisions in the country. For example, in August 2018, an update to the national guidelines introduced new TB drugs for the treatment of pre-extensively drug resistant TB (pre-XDR-TB) taking into consideration the results from the study by Alarcón et. al.[16] on the programmatic management of patients with pre-XDR-TB and results from the study by Cornejo et. al.[19] contributed to the continued use of a regimen for isoniazid-resistant TB.

Operational Highlights

Achievements from the OR program, since its launch in 2008 include:

- TREAT TB has provided more than 150 health professionals in Peru, the Philippines, South Africa, and India with the training needed to conduct high-quality operational research independently.
- TREAT TB also supported a course to build capacity of 20 researchers in India to conduct systematic reviews and in the process, prioritize research activities.
- More than 45 manuscripts have been published and more than 40 abstracts have been presented by participants in the TREAT TB supported training courses.
- In collaboration with TREAT TB partner organizations, The Union and Vital Strategies have also produced several free online educational resources including an interactive e-tool, Introduction to Operational Research,[20] which provides health practitioners and researchers with a foundational overview of OR concepts and practices. This e-tool is available for free on the Vital Strategies website in both English[20] and Spanish.[21]
- Recent work in Peru has led to six participants successfully completing the course; their research focused on several important topics including programmatic management of pre-XDR-TB and TB treatment in children using second-line medications.
- A total of 20 participants were trained in our recent work in The Philippines, and seven participants completed the full training course. Participants presented four abstracts[22, 23, 24, 25] on the shorter regimen and use of bedaquiline for the treatment of MDR-TB at The Union Asia Pacific Regional Conference in Manila in April 2019.

LESSONS LEARNED

Operational research training is complex, and many lessons have been learned on how to optimize research training, including:

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Training courses need to be adapted and tailored to the needs of participants. Research skills vary across settings, and participants' past training and experience. It is important to adapt training courses to fit the local context and meet the needs of participants. Participants may also have competing demands, and the course structure should be designed to accommodate in-person and virtual learning options.

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Collaboration with stakeholders is key to ensure buy in and identification of priority research questions. The design of OR courses and selection of participants should be done in collaboration with key stakeholders, including NTPs, to ensure there is support for the course and identify priority research questions.

—

Training courses are time and resource intensive. Training courses take time to complete, and timelines may not be met due to completing demands of course participants. The publication process is also lengthy and should be considered when designing courses. The ratio of facilitators to participants should also be considered to ensure adequate support is provided for participants.

YALE/MOLDOVA WHOLE GENOME SEQUENCING STUDY

OVERVIEW

2,600

Number of sputum samples sequenced

Whole genome sequencing (WGS) has become an important tool for diagnosis and treatment of TB over the past decade, both for researchers and clinicians. Analyzing the genome of *Mycobacterium tuberculosis* strains can identify specific elements of the bacteria, which can then be used to explore susceptibility to drugs and to study transmission. WGS can therefore enable rapid detection of TB outbreaks and better define transmission patterns thus improving the effectiveness of public health interventions aimed at controlling and preventing the spread of TB.[26]

TREAT TB supported the Yale University School of Public Health in collaboration with the Center for Health Policy and Studies, the Phthisiopheumology Institute in Moldova, and partners, to conduct a three-year prospective observational study in Moldova to evaluate universal whole genome sequencing of *Mycobacterium tuberculosis* to inform public health decisions. The study was initiated in early 2018 and was completed in 2021.

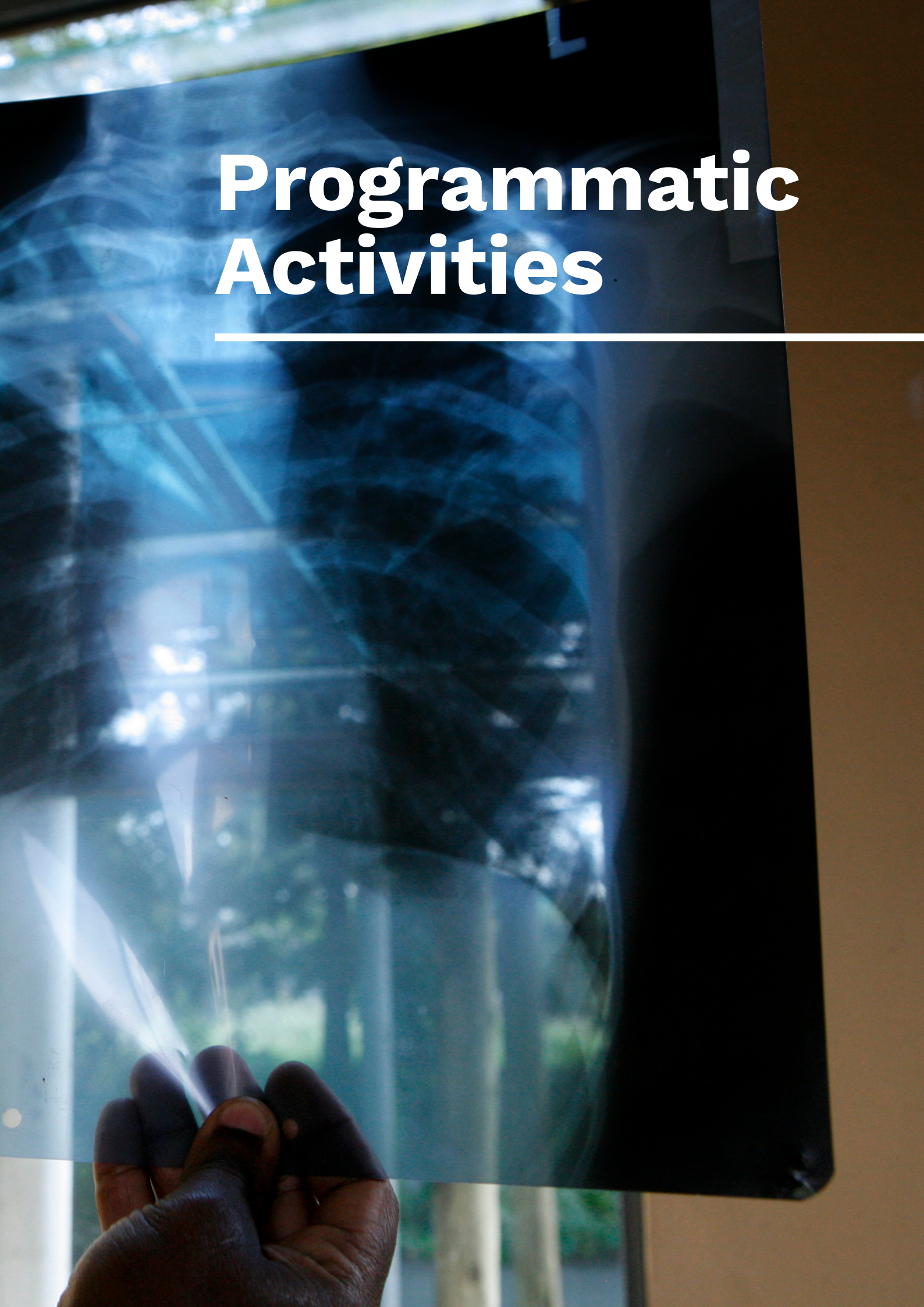
The Republic of Moldova is a small country in Eastern Europe with a disproportionately large TB epidemic. The incidence of TB in Moldova was estimated at 152 per 100,000 in 2015, one of the highest in the European Region, and the incidence of MDR-TB is among the highest in the world. In 2015, 32% of new cases and 69% of retreatment cases in Moldova were MDR-TB.[15]

By combining WGS from all culture-positive samples within Moldova with spatial, epidemiologic, demographic, and laboratory information, this study aimed to achieve several goals:

- To fully characterize TB transmission patterns within Moldova.
- To better understand the relative contribution of acquired and transmitted resistance to the MDR-TB epidemic in Moldova.
- To understand how WGS can be used to inform the rational targeting of TB interventions.
- To build local capacity for interpreting WGS data and understanding its capacity to inform local responses.
- To estimate costs and explore the feasibility of routine use of WGS within the Moldovan TB program.

ACTIVITIES AND ACHIEVEMENTS

This study constitutes the first attempt to use WGS to fully understand TB transmission at the level of an entire high incidence country and to inform targeted interventions. Between January 2018 and December 2019, 2,600 sputum samples were collected for WGS, surpassing the study target of 1,800 samples. The study also provided an opportunity to evaluate costs of diagnosing TB in Moldova and results were published in the *International Journal of Tuberculosis and Lung Disease*[27] in March 2021. Two additional manuscripts, including detailed maps that combine spatial and genomic information to reveal geographic patterns of transmission of TB and MDR-TB across Moldova and costs of WGS in the Moldovan setting will be shared in peer-reviewed publications. These results will contribute important information on the use of combining pathogen genomic, spatial, epidemiological, demographic, and laboratory information to characterize existing TB transmission patterns and better understand the relative contribution of acquired and transmitted resistance to the MDR-TB epidemic in Moldova.



Programmatic Activities

PHILIPPINES TECHNICAL ASSISTANCE

OVERVIEW

From October 2016 to March 2019, TREAT TB provided a comprehensive package of technical assistance (TA) to the Philippines NTP to support national scale-up of the standard short treatment regimen (SSTR) for MDR-TB. TB is a major public health problem in the Philippines, and MDR-TB is a particular challenge, with an estimated 18,000 cases in 2018.[28] Treatment outcomes for MDR-TB are typically worse than those for patients with drug-sensitive TB, in significant part due to the length of treatment and the potential for adverse effects from second-line medications. The partnership with the Philippines NTP was instrumental for the country's scale-up of the SSTR, and strengthening the NTP's supervision, monitoring and evaluation (SME) system. The project aimed to link international best practices and research results into practice for new treatment regimens.

ACTIVITIES AND ACHIEVEMENTS

Key areas of focus were as follows:

Technical assistance

In October 2016, when TREAT TB began its activities in the Philippines, patients with MDR-TB were treated with the standard 20-month regimen, and approximately 50% were successfully treated.[15] After piloting a shorter treatment regimen for MDR-TB, the NTP implemented its plan to scale up the SSTR under programmatic conditions in January 2017. Through onsite technical assistance, TREAT TB worked with the NTP to identify tailored solutions to barriers and challenges with scale up of the SSTR.

300

Number of nurses trained

The TREAT TB team conducted five technical assistance visits in seven regions with staff from national, regional, and provincial/city NTP offices. They provided in-person supportive supervision, and mentorship on the clinical management of MDR-TB for approximately 125 healthcare workers at more than 25 health facilities. In addition, six workshops were conducted with key stakeholders from the national and subnational levels to identify tailored solutions for challenges associated with the scale-up of the SSTR.

By the end of 2017, the SSTR was rolled out nationwide, and by the end of 2018, 80% of patients enrolled in treatment were treated with the SSTR.

Supervision, Monitoring and Evaluation System

A well-functioning SME system can generate relevant information about program performance and has the potential to significantly improve outcomes for MDR-TB. TREAT TB conducted an assessment of the NTP's SME system to identify strengths, gaps, and areas for improvement. A key finding from the assessment was a need to routinely assess quality of routinely collected program data to improve reliability of data-driven decision-making. With the support of key partners including the WHO country office, TREAT TB developed and piloted a routine data quality assessment tool in three regions, which together, accounted for nearly 50% of the MDR-TB burden in the country. The tool aimed to help the NTP easily assess the quality of paper-based forms and implement interventions to improve the accuracy, completeness, and consistency of paper-based data. In addition, TREAT TB also provided inputs on the NTP's monitoring and evaluation (M&E) guidebook, and developed an interactive dashboard for the NTP to monitor implementation of the SSTR. A series of brownbag sessions were also conducted to strengthen capacity of NTP staff to strengthen their data analysis and data visualization skills.

Results from the SME system pilot were presented to the NTP and partners in March 2019 with plans to adapt the tools for use by the NTP and partners.

Training

The TREAT TB team trained more than 300 nurses on the SSTR and management of common adverse drug reactions associated with MDR-TB treatment. As nurses are the frontline healthcare workers, strengthening their capacity to treat patients with MDR-TB will have a major impact on MDR-TB outcomes.

During the 2.5-year project, the NTP has effectively scaled up the shorter regimen and achieved significant progress to improve outcomes for patients with MDR-TB.

Dr. Chen-Yuan Chiang
Consultant with The Union and technical lead for TREAT TB activities in the Philippines

LESSONS LEARNED

TREAT TB's experience with provision of a comprehensive TA project in the Philippines yielded valuable lessons.

125

Number of health professionals who received supportive supervision and mentorship

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Important to engage stakeholders at all levels and identify solutions based on local context. Programmatic management of MDR-TB and implementation of new TB regimens such as the SSTR is challenging partly due to the limited engagement of the health sector at the subnational level and limited capacity and resources at decentralized health centers to manage patients with MDR-TB. However, the traction gained during TREAT TB's TA project was largely due to engagement of all stakeholders. TREAT TB identified the importance of strengthening capacity at all levels to improve programmatic and clinical management of MDR-TB. Through our TA visits and clinical management trainings, we capacitated physicians, nurses, provincial/city coordinators, regional and national staff through the various activities, and our work was done through early and continuous collaboration with key institutions including the NTP and local partners.

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Strengthen capacity at all levels to improve programmatic and clinical management of MDR-TB. TREAT TB aimed to strengthen capacity at the national, regional and provincial/city levels. Through our TA visits and clinical management trainings, we capacitated physicians, nurses, provincial/city coordinators, regional and national staff to ensure capacity to diagnose, treat, and manage MDR-TB was strengthened at all levels of the health system. Coordination between all levels of the system also ensured implementation of national policies at the subnational level.

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Collaboration with all partners is key to harmonize activities. TREAT TB's TA in the Philippines would not have been possible without the early and continuous collaboration with key institutions such as the NTP and partners. Participation in USAID and NTP harmonization activities allowed the project to re-adjust and re-focus its activities and resources accordingly to ensure roles and responsibilities of all stakeholders were complementary rather than duplicative.

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Focus on a "change" indicator. At the onset, TREAT TB focused on one indicator – treatment interruption. This helped the team focus its objectives for all the activities particularly the TA visits. The creation of the signal-alert-alarm-crisis framework enabled the NTP and partners to better track treatment interruption and provide tailored support to patients before they became lost to follow up.

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Strategies should reflect realities on the ground e.g., decentralization, capacity of nurses and doctors in new SSTR facilities. TREAT TB conducted TA activities in seven regions and visited a variety of facilities. This provided a comprehensive perspective on implementation of the SSTR and management of MDR-TB, helped identify good practices, and challenges in different settings. Thus, during our visits and workshops, TREAT TB involved participants from all levels of the system to identify their common concerns and identify unique solutions that would help them achieve zero treatment interruption, and ultimately improve MDR-TB outcomes.

RIGHT
Dr. Chen-Yuan Chiang from The Union discusses programmatic implementation of the shorter treatment regimen for MDR-TB with regional NTP staff in the Philippines

GLOBAL CONSULTATIONS ON TB AND MDR-TB RESEARCH

OVERVIEW

TREAT TB not only added to scientific knowledge through our research activities, but also grew the knowledge base globally within the broader TB community through dissemination of research results and consultation with key stakeholders. TREAT TB specifically set objectives to:

- Map out the TB research landscape in terms of new treatments; and
- Bring key players and stakeholders together to foster collaboration and minimize gaps in communication and coordination with an aim of harmonizing efforts of various research groups.

ACTIVITIES AND ACHIEVEMENTS

The above objectives were pursued through a number of initiatives and networks including:

The Global MDR-TB Clinical Trials Landscape Meeting

TREAT TB worked with other research consortia such as the Research Excellence to Stop TB Resistance (RESIST-TB) and the Singapore Programme of Research Investigating New Treatments for Tuberculosis to coordinate global and regional consultations, bringing together researchers and experts to share experiences and insights on moving forward the agenda on development of new treatments for TB.

The Global MDR-TB Clinical Trials Landscape Meeting, a two-day event in December 2014, sponsored by TREAT TB and RESIST-TB, convened over 60 international MDR-TB experts, including clinical trialists, policymakers, activists, and other stakeholders in the MDR-TB research field. The meeting was held simultaneously in Washington DC, USA, and Cape Town, South Africa, linked by videoconferencing to facilitate face-to-face interaction. The main aims of the meeting were to:

- Devise a coordination strategy to ensure ongoing and future clinical trials were complementary and not duplicative;
- Discuss the potential for standardizing the methodology used in these trials; and
- Discuss the new combinations that were under evaluation and identify other promising new regimens.

A key output of this meeting included a special supplement providing greater detail on individual topics published in the *International Journal of Tuberculosis and Lung Disease*[29] in December 2016. TREAT TB also published a manuscript in *BMC Proceedings*[30] outlining important issues in trial design (such as selecting an appropriate patient population, choice of control regimen, duration/ frequency of follow-up including safety related monitoring and follow-up).

The Global MDR-TB Clinical Trials Landscape Meeting was timely in several regards – at the time of the meeting, no prospective phase III randomized clinical trials of MDR-TB treatment had been completed (although three were underway), while several others were either about to start or were in late design stages.

The presentations at the meeting and the discussions that followed (summarized in the articles published in a supplement as noted above) led directly to a few phase II and III clinical trials, some of which are completed and others underway.

In June 2016, TREAT TB supported a Pediatric MDR-TB Clinical Trials Landscape meeting to provide an update on the pediatric MDR-TB trial landscape and discuss issues related to clinical research of MDR-TB in children. A publication on challenges and opportunities for pediatric MDR-TB clinical trials was published in the *International Journal of Infectious Diseases* in March 2017.[31]

A-TRACTION Network

The Asian Tuberculosis Research and Clinical Trials Integrated Organizational Network (A-TRACTION) was envisaged as a region-wide initiative to facilitate TB clinical research integration and collaboration. The backbone of the collaborations and the network is clinical sites in Asia with TB research experience and laboratory infrastructure to conduct high quality clinical trials.

The inaugural A-TRACTION meeting was held over 1.5 days in March 2018 in Singapore, attended by over 30 TB clinical researchers from 13 countries (Cambodia, China, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Russia, Singapore, Taiwan, Thailand, Vietnam). Following this inaugural meeting, A-TRACTION established a Network Steering Committee comprising of 15 experienced TB clinical researchers from all over Asia to serve as the primary governance structure for the network with the responsibility for development and approval of all policies related to the network's activities, including the establishment of requirements for operations, and ongoing monitoring and evaluation.

In September 2018, a Project Development meeting was held in Singapore with support from TREAT TB. Ten TB clinical researchers came together to brainstorm on collaborative TB clinical trials, designed not only to address important clinical questions, but specifically, trials that would involve multiple Asian sites and countries within the network. The group put forth two proposals to the Joint Global Health Trials scheme, funded by the UK Medical Research Council and the Wellcome Trust.

The meetings directly resulted in the capacity building of the network from the ideation stage all the way to research proposal development and grant applications. In addition to sharing of research/activities in different countries, the meetings presented opportunities for network members to collaborate and participate in other regional initiatives, offer learnings to design their own trials, and explore and further collaborations between different country-specific trial networks as well as TB programs.

In the future, the network is thought to benefit trial sponsors through a structured platform to conduct clinical trials more efficiently, benefit network members via capacity building through human capital development, strengthen infrastructure to conduct clinical trials, and eventually, reduce the burden of TB in the region.

TB MODELING

OVERVIEW

Modeling is an innovative approach to generate valuable evidence for TB stakeholders and policy makers worldwide. Mathematical models can increase the reach and efficiency of research activities to better understand the local epidemiologic burden and the optimal programmatic and policy pathways.

ACTIVITIES AND ACHIEVEMENTS

The following modeling initiatives were successfully implemented during the TREAT TB project:

- TREAT TB partners at the Liverpool School of Tropical Medicine (LSTM), National Taiwan University, and Harvard University School of Public Health designed a novel modeling approach that links transmission modeling with operational modeling. They published a paper in the *International Journal of Tuberculosis and Lung Disease*[32] describing how this model could be used to support the selection and implementation of new diagnostic tools for tuberculosis. This model was then applied to real-world situations in Tanzania in 2011. The results were useful to the NTP in Tanzania, which later used this model to guide decisions related to the roll out of GeneXpert (Cepheid, Sunnyvale, CA, USA). Additional lessons learned and project outputs are described in the TREAT TB Description of Research Outputs 2009–2014 document.[33]

- The London School of Hygiene and Tropical Medicine (LSHTM) developed the Tuberculosis Impact Modelling & Estimates (TIME) model to improve TB care and prevention in low- and middle-income countries by strengthening policies and enabling local capacity building. TIME includes a package of modules, including the ability to quantify current burden of TB in a given setting and how it might change in the future based on planned NTP activities. Through TREAT TB, additional country support was provided, and capacity was strengthened through training and both international and domestic TA to ensure effective absorption of the Global Fund (GF) and other TB funding.

  The TREAT TB-TIME collaboration contributed substantially to TB policy making in a range of high-priority countries, including Nigeria, Vietnam, Indonesia, Ethiopia, and Ghana. Overall, the TREAT TB support was highly successful in achieving its main aims of applying TIME to inform TB policy in selected high priority countries; building capacity in key countries to ensure sustainability of project efforts; and develop, pilot and release new functionality in TIME.

  The KNCV Tuberculosis Foundation has taken over implementation of the TIME modeling framework to ensure future access and sustainability of this modeling initiative.

- LSTM has developed a 9-month, injectable-containing treatment pathway model for Ethiopia, Uganda and India. The model sets out the journey a patient makes in those countries to receive MDR-TB treatment. Cost data from STREAM Stage 1 for Ethiopia have been used, complemented by literature cost data for India and Uganda. Different directly observed therapy (DOT) strategies have been considered, including DOT at the health facility, video-DOT, and 99DOTS.

Publications related to the modeling initiatives can be found in the Appendix.

THE GLOBAL FUND TUBERCULOSIS IN-COUNTRY ADVISORS PROJECT

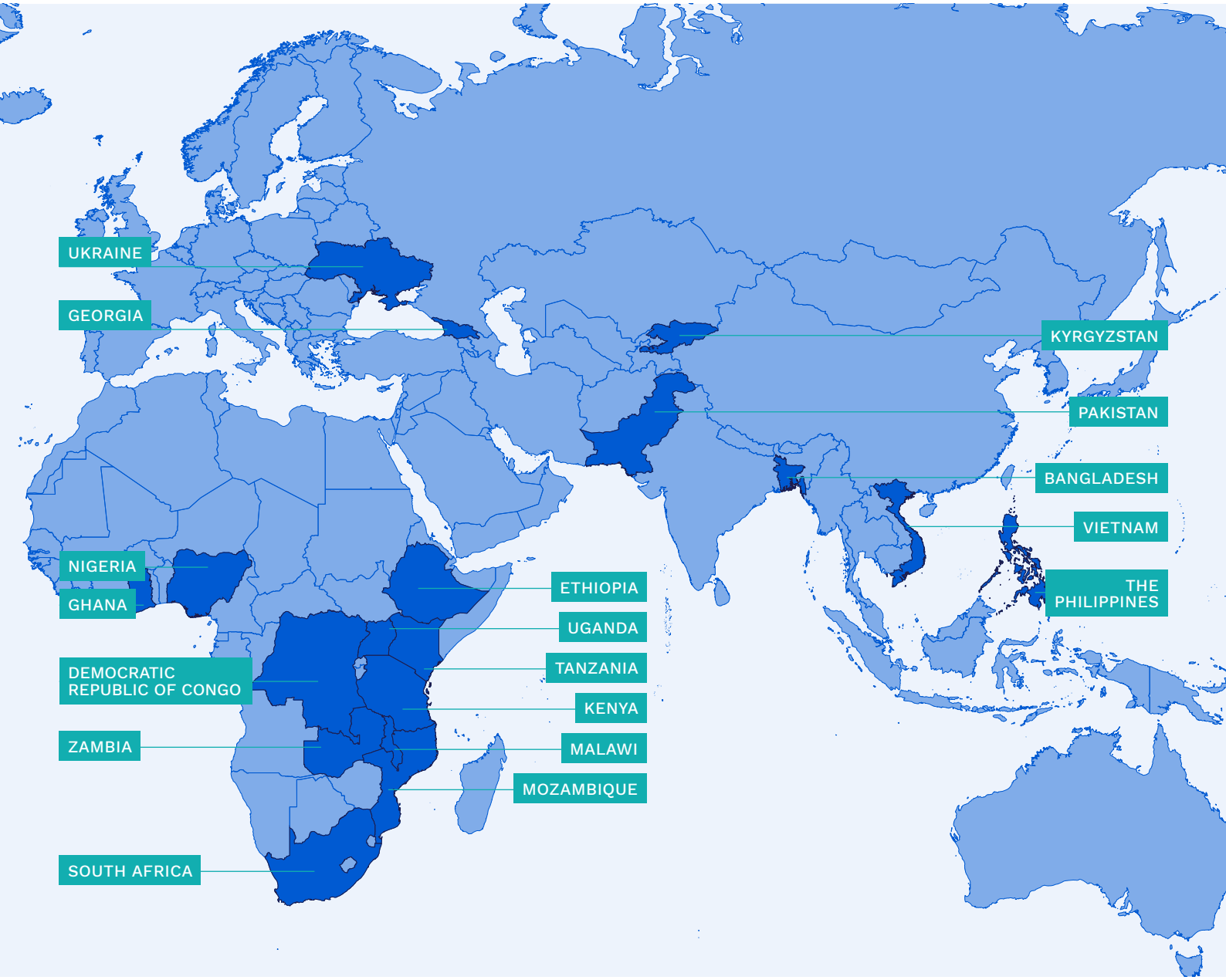
OVERVIEW[34]

Since 2013, USAID has provided funding through the Global Fund (GF) Tuberculosis In-Country Advisors Project to embed senior advisors in NTPs in USAID TB priority countries. The goals of the project were to improve the grant implementation of the Global Fund and to strengthen NTPs' capacity to meet global targets in TB elimination, particularly those related to MDR-TB, and the project also expanded to other technical areas according to the needs of each country.

BELOW
USAID TB priority countries selected in the Global Fund Tuberculosis In-Country Advisors Project

The GF TB Advisor Project grew from the first advisor placed in the Philippines in 2013, to a total of 22 advisors who supported 18 countries over the course of the project.

Advisors have worked in the following countries: Bangladesh, Democratic Republic of Congo, Ethiopia, Ghana, Georgia, Kenya, Kyrgyzstan, Malawi, Mozambique, Nigeria, Pakistan, the Philippines, South Africa, Tanzania, Uganda, Ukraine, Vietnam, and Zambia.



ACTIVITIES AND ACHIEVEMENTS

The project's main activities aimed to improve capacity of in-country partners to effectively implement GF grants through targeted TA; identify any TA needs that the NTP may have, and work with USAID and other partners to fill these needs; and provide continuous, in-country day-to-day support to the NTP on National Strategic Programs and GF grant implementation.

The MDR-TB advisors organized regular discussions with the GF country teams, USAID, and country stakeholders to ensure alignment of technical approaches in the respective TB portfolios. Additionally, the project monitored the progress of grant implementation through field visits; reviewed and analyzed GF grant data and performance reports submitted to the GF and other partners; identified any issues that may have resulted in disbursement delays and suggested appropriate solutions.

Through this initiative, TREAT TB improved access to high-quality, patient-centered services for TB, drug-resistant TB, and TB-HIV to address challenges to access such as cost of services, distance to facilities, hours of operation, and social stigma. By doing so, this likely contributed to decreased TB transmission and progression of latent TB infection (LTBI), through early diagnosis and effective treatment.

Project achievements included:

- The utilization of GeneXpert in Bangladesh increased through addressing bottlenecks identified through routine data analysis and observations from field visits. The project developed and disseminated guidance on medical history taking of previous treatment and prepared a NTP circular on compulsory history taking before initiation of treatment in Bengali in consultation with key partners including the WHO and NTP.
- In Ghana, an intensified TB case finding system was implemented which consisted of systematic screening of all facility attendants for TB in 90 health facilities in 90 priority districts in 2015 and this was gradually scaled up to 1,126 health facilities in 2019. An active TB case finding system in 21 small scale mining districts resulted in an increase in DR-TB case notification from 93 patients in 2014 to 266 patients in 2019.
- By helping countries identify populations at high risk of TB and strengthening health systems through drug policy and management, M&E systems, and human resource development, the project strengthened key service delivery platforms and country commitment and capacity to plan, finance, and implement effective TB solutions.

LESSONS LEARNED

USAID evaluated the advisor project in May 2019, making a number of observations. They concluded (among other things) that technical support, in addition to the advisors, may be needed at NTPs; multiple advisors may be needed (depending on NTP needs); early stakeholder involvement in advisor placements is helpful; and transparent advisor/stakeholder communication is essential.[34]

To read more about USAID's findings related to the advisors project please click here.

PRE-2015 WORK

Information about key TREAT TB activities from the start of the project in 2008 through 2014, including Policy Relevant Outcomes from Validating Evidence on Impact (PROVE-IT) and the Operational Research Assistance Program is available in the TREAT TB Description of Research Outputs 2009–2014 document.[33]

CONCLUSION

More than a decade ago, TREAT TB set out to contribute new knowledge to address key challenges facing the global TB community. At the heart of the mission was the STREAM clinical trial, which has since generated high-quality evidence and influenced policy and program decisions about the use of shorter treatment regimens for MDR-TB at both the global and national level. In addition, TREAT TB has produced or supported an extensive range of published research, analyses and learnings covering topics including diagnosis, treatment and prevention of TB, inlcuding drug-resistant TB, as well as practical learnings in how to carry out and improve research into TB.

Beyond this contribution to knowledge, TREAT TB's legacy has been to build the capacity for research and for implementing TB programs in the places where it worked – often locations with a high burden of TB or MDR-TB and a limited capacity for TB research. Clinical trial institutions are stronger after STREAM and will make future TB trials easier to conduct at STREAM sites. We attribute this in part to USAID's unwavering support for TREAT TB's capacity building and sustainability-focused efforts. TREAT TB's OR training has led to a larger pool of health professionals able to independently undertake locally relevant OR leading to improved health services. Through the STREAM CABs, community members are better able to participate as equal partners in clinical research and communities are better informed about TB and research.

Underpinning TREAT TB's many achievements is an approach that has collaboration at its core. Ending TB, and especially MDR-TB, is difficult and complicated. Robust and meaningful research is a lifeline in this journey, but it only happens when many different stakeholders find a way to work together. This is not always easy, but it is essential. The work of TREAT TB has shown that everybody has a role to play – including governments, communities, health professionals and scientists. In this way, current research findings will become practical parts of TB diagnosis, treatment and prevention, and future research will grow from what TREAT TB has done. With the collaboration of those stakeholders, TREAT TB's work can influence development of better treatment guidelines and programs, and provide a foundation for new research needed to finally end TB.

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APPENDICES

TREAT TB DESCRIPTION OF RESEARCH OUTPUTS 2009–2014

TREAT TB. TREAT TB Description of Research Outputs 2009–2014. International Union Against Tuberculosis and Lung Disease; 2014.

PUBLICATIONS AND RESOURCES

STREAM Clinical Trial

Publications

Phillips PPJ, Van Deun A, Ahmed S, et al. Investigation of the efficacy of the short regimen for rifampicin-resistant TB from the STREAM trial. *BMC Med*. 2020;18(1):314. doi:10.1186/s12916-020-01770-z

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